

Clinical Characteristics and Outcomes of Tuberculosis Infection in Adult Patients with MDS

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Abstract

Background and aim Despite the high incidence of tuberculosis infection (TBI) in patients with hematological diseases, there were few researches on TBI in MDS patients. We retrospectively analyzed the characteristics of MDS patients with TBI in our center to improve the clinical diagnosis and treatment of these patients.

Methods Primary MDS patients diagnosed between 2014 and 2019 at the First Affiliated Hospital of Zhejiang University were retrospectively reviewed, TBI was diagnosed by positive culture(s) or acid fast bacilli on modified Ziehl-Neelsen staining on clinical samples as well as compatible symptoms and signs.

Results Thirty-four of 1347 MDS patients were diagnosed with TBI, nine patients had blast $\geq 5\%$, twelve patients were MDS with excess blast-1 (MDS-EB1), and the rest 13 patients were MDS with excess blast-2 (MDS-EB2). Ten patients had lower risk (low and intermediate) and 24 patients had higher risk (high and very high) according to revised international scoring system (IPSS-R). Moreover, fifteen patients were classified into synchronous group (defined as TBI occurring within 3 months of MDS diagnosis), and the rest 19 patients were non-synchronous group (defined as TBI developed after MDS more than 3 months). Patients in synchronous group have higher rate of persistent fever (11/15 vs. 7/19, $p=0.03$), higher risk classification (14/15 vs. 8/19, $P=0.002$), and higher tendency to transform to acute myeloid leukemia (AML) (8/15 vs. 4/19, $P=0.04$) than those in non-synchronous group. The median time to AML was significantly shorter in synchronous group (7.68 months vs. 23.83 months, $P<0.01$). Most patients received regular anti-tuberculosis treatment (ATT)(33/34) and support care(22/34) for MDS, patients received support care were more prone to proceed to AML than those received active therapy such as decitabine (12/22 vs. 2/12, $P=0.03$). The median OS of all patients in synchronous group was just 14.17 months, while in non-synchronous group, it was 34.07 months ($P = 0.01$). However, treatments for MDS had no effect on OS($P=0.67$).

Conclusion TBI is not uncommon among patients with MDS, patients with synchronous TBI and MDS progress faster and have shorter OS, which may be associated with genetic susceptibility and lack of active therapy.

Background

Myelodysplastic syndromes (MDS) is a group of clonal hematological stem cell disorders, manifested as persistent cytopenia, accompanied by innate humoral and cellular immune-paresis[1, 2]. As a result, these patients are prone to various new infections and reactivation of latent infections including TB[3–5]. With the increasing incidence of cancer and the advance in treatment, opportunistic TBI has indeed increased significantly in cancer patients recently [6, 7], especially in hematological malignancies [8–11]. A large-scale clinical retrospective study in Taiwan found that the rate of TBI in patients with hematological malignancies ranking second [12], with an incidence rate of 3.7%. In another research by Ganzel C et al

found that among patients with hematological tumors, MDS and lymphoma patients have the greatest risk of TBI [13], the hazard ratio was highest (2.74, $P = 0.012$ and 2.70, $p < 0.001$). These researches encourage a heightened awareness for TBI among patients with a background of MDS. However, only sporadic reports of TBI in MDS patients have appeared until now [14–16].

Here, we retrospectively analyzed 34 patients with MDS and TBI and try to investigate the characteristics and outcomes thus providing experience for the clinical diagnosis and treatment of TBI in MDS patients.

Methods

Patients

This retrospective study included all primary MDS patients with TBI between January 2014 and December 2019. All medical records of the identified cases were retrieved and systemic analysis of characteristics pertaining to MDS, treatment, organs involved with TBI was conducted. This study was approved by the Ethics Committee of the First Affiliated Hospital, College of Medicine, Zhejiang University.

Definition and diagnosis of TBI

TBI was considered if it fulfilled one of the following criteria: 1, Modified Ziehl–Neelsen staining on clinical samples (sputum, body fluids, fine needle aspirate or antemortem/postmortem biopsy) as well as epithelioid granuloma and caseous necrosis, or culture was positive, 2, clinical symptoms and typical radiologic characteristics such as cavitation, lymphadenopathy and effusion were presented, 3, response to ATT and no evidence of alternative bacterial or fungal etiology based on cultures or serologic tests. Interferon- γ release assay was also used to further identify TB infection. Response to ATT was defined as resolution of fever and resolution of lesions by radio-logic image after institution of ATT. Synchronous infection was defined as a diagnosis of TB disease within 3 months of MDS diagnosis[17-19]

Statistical analysis

All statistical analyses were performed using SPSS 22.0 (SPSS, Chicago, IL, USA). Chi-square and Fisher's exact test were used for Categorical variables, while the Student's t-test or ANOVA test were used for Continuous variables. OS was measured from the date of diagnosis of MDS to the date of death or last follow-up, the survival stratified by synchronous and non-synchronous of MDS and TB infection was analyzed by Kaplan-Meier method and log-rank test. The significance level was set at 0.05 and all p values were two-tailed.

Results

1, Epidemiology of tuberculosis infection

Between 2014 and 2019, a total of 1347 patients were diagnosed with MDS in our center, including 113 patients were MDS with single lineage dysplasia (MDS-SLD), 9 patients were 5q- syndrome, 209 patients

were MDS with multi lineage dysplasia (MDS-MLD), 94 patients were MDS-unspecified (MDS-U), 416 patients were MDS with excess blasts 1 (MDS-EB1), and the rest 407 patients were MDS with excess blasts 2 (MDS-EB2). Among them, thirty-four patients were diagnosed with TBI. The overall incidence of TBI in patients with MDS during the study period was 2.5 %, and the numbers of TB cases among each WHO subtype of MDS were as follows: SLD, n = 2 (1.77%); MLD, n = 5 (2.39%); MDS-U, n = 2 (2.13%); MDS-EB1, n = 12 (2.88%); MDS-EB2, n = 13 (3.19%); Patients with MDS-EB seemed more likely to develop TBI than patients with other sub-type (3.04% vs. 2.1%, p = 0.334; odds ratio, 1.45; 95% confidence interval, 1.39- 4.41) but the difference was not significant.

2, Clinical and laboratory characteristics of patients with tuberculosis infection

Among 34 patients diagnosed with MDS and TBI during the period of study, male to female was 24:10 median age was 61 years old, 18 had intermediate-1, 13 had intermediated-2, and 3 had high risk according to IPSS risk. When classified through IPSS-R, 2 patients had low, 10 had intermediate, and 15 had high risk, while the rest 5 had very high risk. Moreover, fifteen patients were synchronously diagnosed with TBI and MDS and the rest 19 patients were developed TB after MDS more than 3 months (non-synchronous).

Persistent fever appeared in almost all patients and most were high fever without regular type, other clinical features were not predicative, all patients had no response to general spectrum antibacterial drugs. In synchronous group, only one patient had previous TBI, while in the non-synchronous group, 12 patients had a previous history of TBI. Further analysis showed that patients diagnosed synchronously with TBI were more likely to have higher risk classification (14/15 vs. 8/19, P=0.002), more frequent persistent high fever (11/15 vs. 7/12, P=0.03) and higher tendency to transform to AML (8/15 vs. 4/19, P=0.04). The median time to AML was significantly shorter in the synchronous group (7.68 months) than those in non-synchronous group (23.83 months, P<0.01). However, other clinical characteristics, such as gender, age, blood cell count, and organs involved in TBI, were not significantly different between the two groups. The baseline characteristics of the patients were given and compared in Table 1.

3, Diagnosis of TBI

Only 4 patients (11.76%) had both positive acid-fast bacilli staining of samples including sputum and lymphoid tissue and culture for TB in our study, and 22 patients had just positive tissue staining without culture results. The remaining 8 patients were clinical-radiological TBI. Besides, the interferon- γ release test of all patients in our study was positive. The organ most common involved with TBI was lung, followed by lymph nodes, which were seen in 70.5% (24/34) and 41.18% of patients respectively. TBI occurred only in lung and lymph node in 13 and 9 patients respectively, and 13 (38.24%) patients had pulmonary involvement also had concomitant extra-pulmonary tuberculosis (lymph nodes, 5; Pleural cavity, 4), two patients had lumbar tuberculosis, one patient had TBI of the skin there was no significant difference in organs involved between the two groups.

4, The treatment and outcome of patients with TBI and MDS

Most patients received supportive care for MDS (22/34, 64.71%), eleven patients received decitabine therapy, and only 1 patient received hematopoietic stem cell transplantation (HSCT). For 22 patients received support care, 10 have transformed to AML, but in those received decitabine therapy, only 2 patients proceeded to AML. In synchronous group, 10 patients received supportive care and 5 patients received decitabine therapy, while in non-synchronous group, 12 patients received support care and 7 received active therapy, and there were no significant difference between the two groups.

Thirty-three patients received ATT, among which 26 received standard ATT (isoniazide, rifampin, ethambutol, and pyrazinamide) and 7 (21.2%) patients received fluoroquinolone based ATT. Twenty-four patients had response to ATT, and 9 patients had no response—manifesting as lasting fever, six patients were in synchronous group and 3 in non-synchronous group. Two patients died of TBI without control, and 16 patients died due to MDS progression, among which 9 patients had transformed into AML, and 4 patients died of complication related to treatment. For patients were still alive, 7 have progressed disease, and 3 patients have transformed into AML, 5 patients are still on ATT.

The median OS of all patients was 25.63 [95% CI 12.50-38.76] months (Fig 1A). In synchronous group, it was just 14.17 (95% CI 13.17-15.18) months, while in non-synchronous group, OS was relatively longer, 34.07 (95% CI 13.61-54.53) months (P = 0.01) (Fig 1B). While OS were compared between patients received different treatments, it was 25.63 (95% CI 10.85-40.41) months in support care group, and 29.53 (95% CI 0-59.51) months in patients received decitabine and HSCT (P=0.32) (Fig 1C).

Discussion

Compared with the general population [20], patients with MDS have a higher risk of developing TB infection. Previous studies have found that persistent cytopenia caused by ineffective hematopoiesis and defects in the lymphatic system such as a decrease in the absolute value of T lymphocytes [21], as well as a decrease in the ratio of CD4 / CD8 were main reason [22, 23].

While in real world, TBI were seldom suspected in MDS patients, several reasons may be involved. First, clinical manifestations of MDS with TBI are not specific [24–26], long standing fever with constitutional symptoms, even enlarged lymph nodes is often attributed to MDS itself or progression to acute leukemia [16, 27], as well as other pathogenic microbial infections, such as bacteria and fungi. Second, the limitations of most of the existing diagnostic methods make the exact diagnosis rate of TBI low [28], and severe cytopenias further precludes the use of invasive diagnostic modalities to obtain a definitive evidence for TB [27]. Thirdly, Other serious co-morbidities of MDS have attracted our attention, making us neglect the symptoms of TBI. In our study, some patients showed persistent fever and enlarged lymph nodes in the mediastinum, but due to a significant cytopenia, histological staining could not be performed as soon as possible, which extended the diagnosis time.

As a precursor disease of AML, MDS has similar clinical manifestations with low-proliferative AML, but MDS with TBI is very different from AML. In our study, not all TBI were secondary to MDS treatment, nearly half of TBI were found synchronously with MDS. Further analysis showed that MDS patients with

synchronous TBI have higher risk stratification, higher AML transformation rate, and shorter survival time, suggesting that these patients may have different genetic susceptibility bases. Previous studies have showed that some gene mutations and polymorphisms are associated with susceptibility to MDS, Among which, HLA-DRB1, GATA2 are also associated with TBI susceptibility [29, 30]. Unfortunately, there have not enough data about gene polymorphism and mutation in our retrospective study to further analysis.

MDS combined with TBI could led to the rescheduling of therapy. In our study, most patients had higher risk group, but they received supportive treatment because of combined TBI, and the number of patients who received demethylating drugs and HSCT were lower than the overall patients in the same period, but the AML transformation and disease progression were higher than the overall patients [31], so we speculated that failure to receive active treatment may be one reason for the rapid progression of patients with MDS and TBI. Previous study has found that HMA as a bridge to high dose therapy in AML patients with TBI could be a useful strategy [27], in our study, patients received decitabine also have a lower AML transformation rate (2/11 vs. 10/22, $P = 0.03$), which also suggested that patients may benefit from active therapy.

Conclusions

TBI is not uncommon among patients with MDS, patients with synchronous TBI and MDS progress faster and have shorter OS than those who developed TBI after MDS diagnosis, which may be associated with genetic susceptibility and lack of active therapy.

List Of Abbreviations

MDS myelodysplastic syndrome

TBI tuberculosis infection

AML acute myeloid leukemia

ATT anti tuberculosis therapy

OS overall survival

Declarations

Ethics approval and consent to participate

Ethics and publication of this study was approved by the Ethics Committee of the First Affiliated Hospital, College of Medicine, Zhejiang University on January 30, 2020. The committee waived the requirement for informed written consent due to the retrospective and anonymous nature of the data and the fact that this research presented no risk of exposure to the subjects. Research was conducted in accordance with the 1964 Declaration of Helsinki and its later amendments.

Consent for publication

Not applicable

Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors have no conflicts of interest.

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Authors' contributions

HT and YR designed the study. YR and HT wrote the manuscript. YR, YL, and CM analyzed and arranged the data. GX, CL and LW performed telephone visit of all patients, CH, YR, XZ, LM, WX, YL provided patients' data. JJ guided the project design and article modification.

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Tables

Table 1 Patient characteristics according to the time of TBI occurred during the process of MDS

| Patient characteristics | Total patients | Synchronous(N=15) | Non-Synchronous(N=19) | P value |
|-----------------------------------|----------------|-------------------|-----------------------|---------|
| Median age | 62(17-84) | 59(17-84) | 64(27-84) | 0.85 |
| Gender(M:F) | 24:10 | 11:4 | 13:6 | 0.75 |
| Neutrophil count | 0.85(0.2-4.6) | 0.7(0.2-4.6) | 1.2[0.3-1.9] | 0.17 |
| Hemoglobin | 81.5(27-126) | 73(37-121) | 84(27-126) | 0.34 |
| Platelet count | 43(4-128) | 36[4-125] | 54[5-128] | 0.43 |
| Blast(%) | 7(0-16) | 9(0-14) | 5.5(0-16) | 0.16 |
| IPSS risk | | | | 0.30 |
| Lower risk(low and int-1) | 17 | 6 | 11 | |
| Higher risk(int-2 and high) | 17 | 9 | 8 | |
| IPSS-R risk | | | | [0.05] |
| Lower | 10 | 1 | 9 | |
| Higher[high and very high) | 24 | 14 | 10 | |
| Organs involved | | | | 0.49 |
| Lung | 13 | 4 | 9 | |
| Lymph node | 9 | 5 | 4 | |
| Other organs | 3 | 1 | 2 | |
| Concomitant lungs and other organ | 9 | 5 | 4 | 0.98 |
| Previous history of TB | 13/34 | 1/15 | 12/19 | [0.05] |
| Persistent fever | 18/34 | 11/15 | 7/19 | 0.03 |
| Ferritin | | 680.9[110.8-4163] | 572.9[108.8-7130.9] | 0.25 |
| AML transformation | 12/34 | 8/15 | 4/19 | 0.04 |
| Median time to AML | | 7.68 | 23.83 | [0.05] |
| outcome | | | | 0.06 |
| dead | 19 | 11 | 8 | |
| alive | 15 | 4 | 11 | |
| Treatment | | | | 0.67 |

| | | | |
|--------------|----|----|----|
| Support care | 22 | 10 | 12 |
| DAC | 11 | 5 | 6 |
| HSCT | 1 | 0 | 1 |

Table 2 Patient characteristics according to treatment for MDS

| Patient characteristics | Support care | Active therapy | P value |
|-------------------------|--------------|----------------|---------|
| No | 22 | 12 | |
| IPSS risk | | | 0.16 |
| lower | 13 | 4 | |
| higher | 9 | 8 | |
| IPSS-R risk | | | 0.65 |
| lower | 3 | 1 | |
| higher | 19 | 11 | |
| outcome | | | 0.86 |
| alive | 8 | 4 | |
| dead | 14 | 8 | |
| AML transformation | 12/22 | 2/12 | 0.03 |

Figures

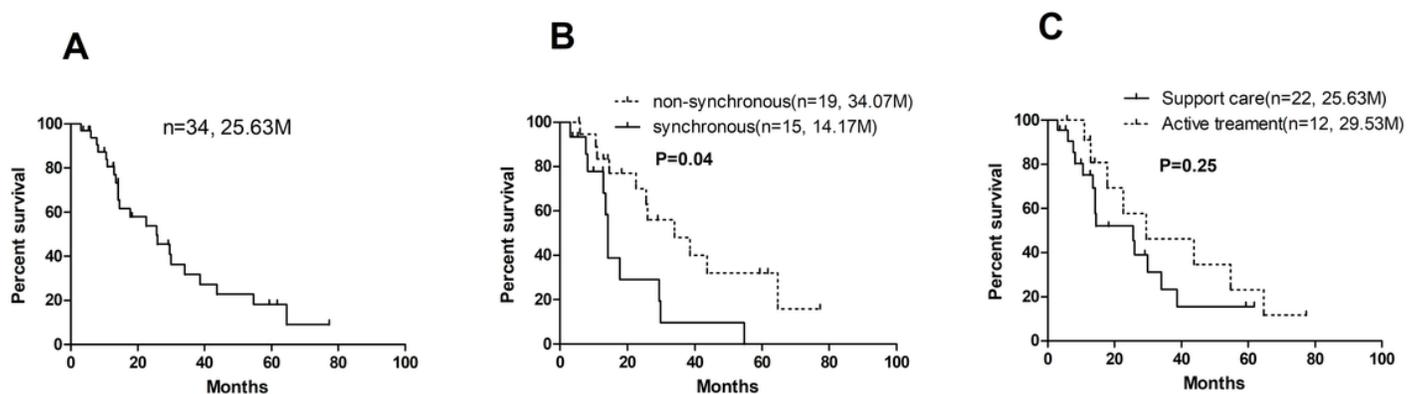


Figure 1

OS of MDS patients with TBI: A Total OS of all patients; B, OS of patients according to time of TBI occurred during process of MDS; C, OS of patients according to treatment.